Letter to the Editors

Terbinafine-associated inhibition of dextromethorphan metabolism in Chinese subjects

Terbinafine is an orally active allyamine antifungal agent that has been newly marketed in China. Abdel-Rahman *et al.* [1] showed that terbinafine was an inhibitor of CYP2D6 activity and as potent as quinidine *in vitro*. A subsequent *in vivo* study confirmed that terbinafine inhibited CYP2D6 activity sufficiently to produce a discordance between genotype and phenotype for this polymorphically expressed enzyme [2]. There was also a case report of nortriptyline intoxication in a patient also taking terbinafine [3]. The genetic polymorphism of CYP2D6 in Chinese differs from that in Caucasians because of the lower prevelance (1%) of poor metabolizers (PM) in the former [4] compared with the latter (5–10%) [5]. The aim of the present study was to determine whether terbinafine inhibits CYP2D6-mediated metabolism in Chinese to the same extent as in Caucasians.

Ten (five men and five women) native Chinese subjects were recruited with a mean age was 24 ± 5 years and a mean weight of 60 ± 12 kg. All were healthy as assessed by blood biochemistry and none smoked tobacco or drank alcohol. Subjects were excluded if they were receiving any medications known to induce or inhibit cytochrome P450. Informed consent was obtained from all subjects. All subjects were genotyped to detect wild type *CYP2D6 (CYP2D6*1)* and the allele possessing the point mutation ($C^{188} \rightarrow T$, *CYP2D6*10*) causing diminished CYP2D6 activity according to a method described previously [6]. Evaluation of CYP2D6 activities at baseline and after terbinafine therapy was performed according to a dextromethorphan phenotyping method [4]. Terbinafine hydrochloride tablets (250 mg) were administered once daily to all subjects for 14 days.

The concentrations of dextromethorphan and dextrophan in urine were measured by a reverse-phase h.p.l.c. method with fluorescence detection developed in our laboratory [7]. Subjects' urinary molar metabolic ratio (MR) was calculated according to the method of Schmid [8]. Subjects with a $MR > 0.3$ were categorized as poor metabolizers (PM), and those with a $MR \leq 0.3$ as extensive metabolizers (EM). Differences in the dextromethorphan MR and urinary recovery before and after pretreatment with terbenafine were tested by using a Student's *t*-test for paired samples. A P value of less than 0.05 was regarded as statistically significant. 95% confidence interval (95% CI) for differences in means were also calculated. Data are reported as mean $\pm$ s.e. mean.

For 10 subjects treated with terbinafine for 14 days, mean MR values were increased from 0.028 ± 0.027–0.321 ± 0.333 (difference: 0.293, 95% CI: 0.072,0.514, $P = 0.015$) with a mean of 15.6 fold increase. Four out of 10 EM subjects were converted to apparent PMs with respect to CYP2D6 (Table 1), indicating a strong inhibitory effect of terbinafine on dextromethorphan metabolism. For CYP2D6 C^{188}/C^{188}, dextromethorphan MR values increased from 0.004 ± 0.001 at baseline to 0.113 ± 0.030 after terbinafine treatment, a 32-fold increment. For CYP2D6 C^{188}/T^{188} and T^{188}/T^{188}, there was about a 10-fold increase in dextromethorphan MR.

Abdel-Rahman *et al.* [2] showed that a mean 97-fold increase in the dextomethorphan MR was observed for six Caucasian extensive metabolizers after 2 weeks' treatment

Table 1 The metabolic ratio, CYP2D6 genotype and phenotype of dextromethorphan in 10 native Chinese subjects before and after 14 days of terbinafine treatment.

		Baseline (n = 2)		*After terbinafine*		
Number	*CYP2D6 genotype*	*MR*	*Phenotype*	*MR*	*Phenotype*	*MR fold*
1	*1/*1	0.004 ± 0.001	EM	0.134	EM	33.5
2	*1/*1	0.003 ± 0.001	EM	0.091	EM	30.3
3	*1/*10	0.029 ± 0.036	EM	0.482	PM	16.6
4	*1/*10	0.006 ± 0.003	EM	0.074	EM	12.3
5	*1/*10	0.018 ± 0.006	EM	0.125	EM	6.9
6	*10/*10	0.025 ± 0.018	EM	0.293	EM	11.7
7	*10/*10	0.038 ± 0.021	EM	0.061	EM	1.6
8	*10/*10	0.055 ± 0.042	EM	0.486	PM	8.8
9	*10/*10	0.015 ± 0.003	EM	0.318	PM	21.2
10	*10/*10	0.090 ± 0.073	EM	1.150	PM	12.7
Mean		0.028		0.321		15.6
s.d.		0.027		0.333		10.1

with terbenafine. For 10 Chinese extensive metabolizers at the same daily dose as in our study the mean fold increase in dextromethorphan MR was six times less. The CYP2D6 alleles associated with poor metabolizers in Caucasians are mainly CYP2D6*3 and CYP2D6*4 (>98%) [9]. However, these alleles are much less frequent (<10%) in Chinese [10]. On the other hand, CYP2D6*10B, a gene copy with a $C^{188} \rightarrow T$ mutation, is predominant in Chinese extensive metabolizers [6] and is associated with decreased CYP2D6 activity. We have found that the mean baseline MR values in the 10 Chinese EM subjects from the present study were about five times as high as that in the six Caucasian EM subjects reported by Abdel-Rahman [2] (0.028 ± 0.027 *vs* 0.006 ± 0.003). Noticeably, there was no significant difference in mean dextromethorphan MR values between the two groups after terbinafine therapy (0.321 ± 0.333 *vs* 0.282 ± 0.076, $P > 0.05$). Therefore, it is not unexpected that the increase in dextromethorphan MR in Chinese is not as high as that in Caucasians after the same terbinafine dose and duration of treatment.

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